Carbanion Arylations

DOI: 10.1002/anie.200704539

Expanding the Synthetic Potential of Asymmetric Deprotonation: Arylation of Carbanions

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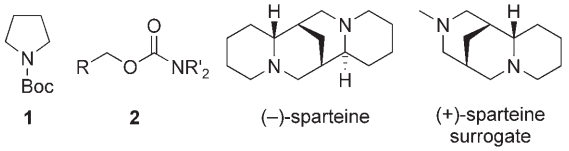
arylations · asymmetric synthesis · carbanions · Negishi coupling · transmetalation

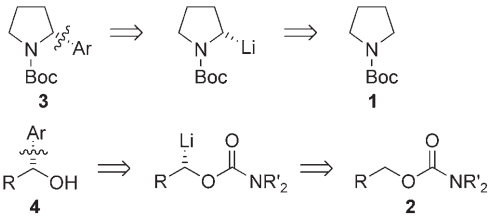
For over 15 years, synthetic organic chemists have had access to enantioenriched carbanions derived from *N*-Boc pyrrolidine **1** (Boc = *tert*-butoxycarbonyl) and *O*-alkyl carbamates **2** upon treatment with a chiral base comprising *s*BuLi and (−)-sparteine (Scheme 1).[1,2] This asymmetric deprotonation



Scheme 1. Carbamates **1** and **2** that give enantioenriched carbanions upon treatment with *s*BuLi and (−)-sparteine. Boc = *tert*-butoxycarbonyl; R, R′ = alkyl.

methodology was pioneered by the groups of Hoppe and Beak,[1–3] and has been supplemented by work in which a readily accessible (+)-sparteine surrogate (Scheme 1) was developed.[4] As a result, deprotonation and electrophilic trapping of carbamates **1** and **2** using *s*BuLi/(−)-sparteine or the (+)-sparteine surrogate can produce either enantiomer of the substituted pyrrolidines or protected secondary alcohols. However, the use of these types of reactions in synthesis has been hampered to some extent by the limited range of compatible electrophiles. A number of these limitations have been addressed by the groups of Dieter[5] and Taylor;[6] transmetalation of the organolithium compound to an organocopper reagent (RCu(CN)Li or $R_2CuLi{\cdot}LiCl$) significantly widens the range of electrophilic partners. However, there can be a loss of some enantioselectivity through these transmetalation processes,[5,7] and until recently it was not possible to arylate enantioenriched carbanions.

This Highlight summarizes two rather different ways of directly arylating enantioenriched carbanions generated from *N*-Boc pyrrolidine **1** and *O*-alkyl carbamates **2**. The methodology facilitates conceptually new disconnections for preparing chiral benzylic amines and alcohols (Scheme 2). Thus,

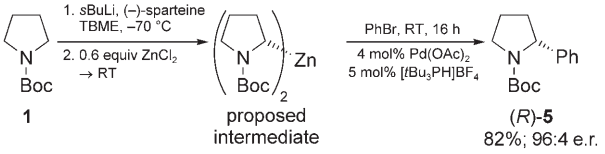


Scheme 2. Retrosynthetic strategies to give arylated carbanion equivalents **3** and **4** from **1** and **2**. Ar = aryl, R, R′ = alkyl.

aryl-substituted pyrrolidines **3** and benzylic alcohols **4** are derived from **1** and **2**, respectively. These seemingly counterintuitive disconnections are made possible by either transmetalation to an organozinc reagent (for **3**) or the use of organoboron intermediates (for **4**), and the absolute stereochemistry is controlled by the *s*BuLi/(−)-sparteine or (+)-sparteine-surrogate chiral base.

The direct asymmetric arylation of *N*-Boc pyrrolidine **1** was developed by Campos and co-workers from the Merck Process Group.[8] Their approach uses Beak's asymmetric deprotonation methodology to give an enantioenriched organolithium which is transmetalated to an organozinc species (either RZnCl, R_2Zn, or R_3ZnLi) before entering into a palladium-mediated Negishi coupling with an aryl bromide. The optimized reaction conditions are summarized in the example shown in Scheme 3. Thus, *N*-Boc pyrrolidine **1** was lithiated using *s*BuLi/(−)-sparteine in TBME at −70 °C, then 0.6 equivalents of $ZnCl_2$ were added, and the reaction was warmed to room temperature. Based on the stoichiometry, it is likely that a dialkylzinc reagent was formed, which then reacted with bromobenzene in the presence of 4 mol % of $Pd(OAc)_2$ and 5 mol % of $[tBu_3PH]BF_4$ to give the arylated pyrrolidine (*R*)-**5** in 82 % yield and 96:4 e.r.

This enantioselective Negishi reaction is notable for several reasons. Although based to some extent on Dieter



Scheme 3. Example of the synthesis of an aryl-*N*-Boc pyrrolidine (Ar = Ph; **5**) from **1**. TBME = *tert*-butyl methyl ether.

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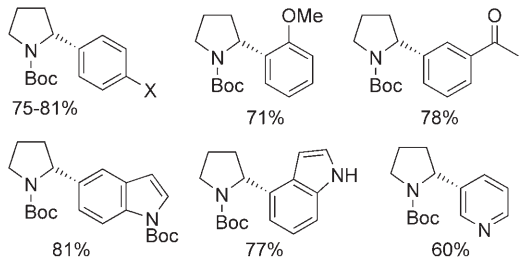
and Li's racemic palladium-catalyzed coupling of lithiated *N*-Boc pyrrolidine with aryl iodides using copper(I) cyanide,[9] the Merck Process Group report the first direct asymmetric arylation of an enantioenriched carbanion. Significantly, the enantioselectivity imparted by the *s*BuLi/(−)-sparteine deprotonation is maintained throughout the whole transmetalation–coupling process. Indeed, Negishi coupling with a less reactive bromopyridine had to be carried out at 60 °C, which indicates that the organozinc reagent is configurationally stable at this temperature. Furthermore, a high yield of the Negishi coupling product is obtained, even though the secondary alkyl ligands on palladium would be expected to undergo facile β-hydride elimination. The conditions presented in Scheme 3 are a comprehensive optimization of both palladium source and ligand. The reaction proceeds smoothly using 1.0, 0.6, or 0.35 equivalents of $ZnCl_2$, suggesting that all types of organozinc reagent (RZnCl, R_2Zn or R_3ZnLi) are compatible with the Negishi step.

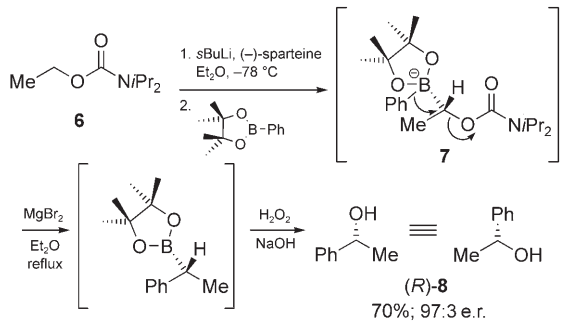
This method was found to be general, which is of synthetic importance, and the range of successful examples included electron rich/deficient aryl bromides, *ortho*-substituted aryl bromides, and heteroaromatic systems (Scheme 4). Even an unprotected bromoindole was successfully coupled. Reaction of the organozinc reagent with 3-bromopyridine at 60 °C delivered a direct precursor to (*R*)-nicotine in 60 % yield.



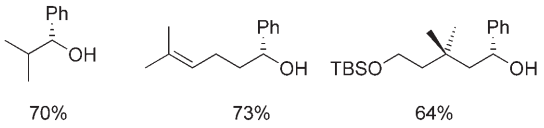
Scheme 4. Examples and yields of successfully synthesized 2-aryl-*N*-Boc pyrrolidines. X = F, NMe_2, CO_2Me.

For the arylation of enantioenriched carbanions derived from *O*-alkyl carbamates **2**, a completely different strategy has been developed. In this case, the enantioenriched carbanion is trapped to give an organoboron intermediate which undergoes a 1,2-metalate rearrangement to a new organoboron compound and, ultimately, forms an alcohol after oxidative hydrolysis of the carbon–boron bond. The 1,2-metalate rearrangement of chiral α-chloroboronic esters was pioneered by Matteson,[10] but it was Hoppe et al.[11] and then Kocienski and co-workers[12] who realized that this approach could be combined with the asymmetric deprotonation of *O*-alkyl carbamates **2**.

Aggarwal et al.,[13] have further optimized the Hoppe–Kocienski method and extended it to new substrates and reactions, including arylation of carbanions and an attractive iterative approach. An example from Aggarwal and co-workers' work, which serves to illustrate the method, is shown in Scheme 5. Thus, *O*-alkyl carbamate **6** was lithiated using *s*BuLi/(−)-sparteine in Et_2O at −78 °C and trapped with an appropriate pinacol-derived boronic acid derivative to give boronate **7**. As Hoppe had appreciated, boronate **7** is equivalent to a Matteson chiral α-chloroboronic ester and can be induced to undergo 1,2-metalate rearrangement upon refluxing in the presence of $MgBr_2$. The newly formed organoboron adduct was then oxidatively hydrolyzed ($NaOH/H_2O_2$) to give alcohol (*R*)-**8** (97:3 e.r.) in 70 % yield. A key feature of this methodology is that the *O*-alkyl carbamate is effectively deprotected to reveal a free hydroxy group during the transformation. Normally, forcing conditions ($LiAlH_4$/reflux) are necessary to cleave such carbamate protecting groups. A range of *O*-alkyl carbamates were successfully employed in this process (Scheme 6) and it was also shown that trialkylboranes could be used. Furthermore, Aggarwal reported that an iterative approach with (−)-sparteine and the (+)-sparteine surrogate could be used to prepare each of the four stereoisomers of a chiral alcohol containing two stereogenic centers, although this did not involve arylation of a carbanion.

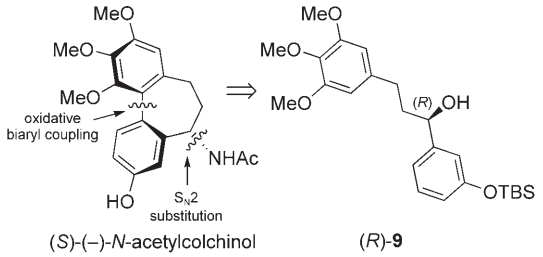


Scheme 5. Synthesis of aryl alcohols from *O*-alkyl carbamates.

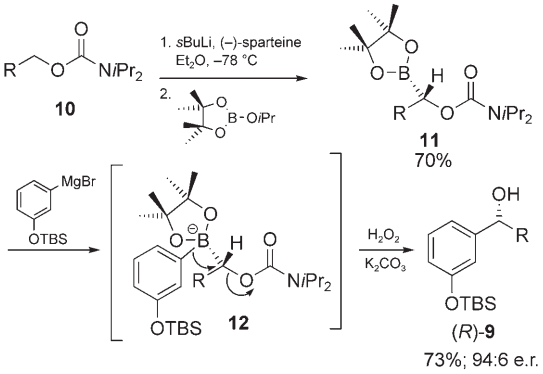


Scheme 6. Examples of alcohols that can be formed from *O*-alkyl carbamates. TBS = *tert*-butyldimethylsilyl.

Prior to Aggarwal's work, Kocienski et al. had already demonstrated the synthetic potential of this type of 1,2-metalate rearrangement with the total synthesis of the tubulin polymerization inhibitor (*S*)-(−)-*N*-acetylcolchinol.[12] Part of the retrosynthetic analysis is shown in Scheme 7: alcohol (*R*)-**9** was used to complete the end-game of the synthesis by an oxidative biaryl coupling and hydroxy activation/S_N2 displacement. The key intermediate (*R*)-**9** should now be recognizable as a product of arylation of an *O*-alkyl carbamate-derived carbanion, and was prepared as outlined in Scheme 8. Asymmetric deprotonation of *O*-alkyl carbamate **10** followed by electrophilic trapping with a borate ester delivered boronate **11** in 70 % yield. Then, in a separate step, boronate **11** was reacted with the required aryl Grignard reagent to generate boronate **12**, which rearranged smoothly to give, after oxidative hydrolysis, alcohol (*R*)-**9** (94:6 e.r.) in 73 % yield (Scheme 8). Alternatively, the required boronate



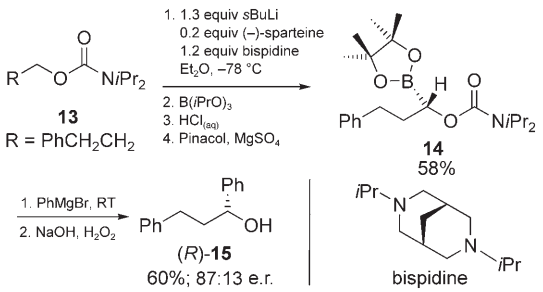
Scheme 7. Retrosynthesis of (*S*)-(−)-*N*-acetylcolchinol from alcohol (*R*)-**9**. TBS = *tert*-butyldimethylsilyl, Ac = acetyl.



Scheme 8. Synthesis of the key alcohol (*R*)-**9** in Scheme 7 from *O*-alkyl carbamate **10**. R = 3,4,5-$(MeO)_3C_6H_2(CH_2)_2$.

12 could be directly accessed in a one-pot procedure along the lines of that shown in Scheme 5 to give a 65% yield of alcohol (*R*)-**9** (98:2 e.r.). Alcohol (*R*)-**9** was then used to complete an elegant synthesis of (*S*)-(−)-*N*-acetylcolchinol. This synthesis is a stern test of the asymmetric deprotonation–1,2-metalate rearrangement method, as the *O*-alkyl carbamate and aryl group are both functionalized.

As a final example, work in our group has combined the Hoppe–Kocienski methodology with catalytic asymmetric deprotonation using substoichiometric quantities of (−)-sparteine (Scheme 9).[14] Thus, deprotonation of *O*-alkyl carbamate **13** was achieved using 1.3 equivalents of *s*BuLi, 0.2 equivalents of (−)-sparteine, and 1.2 equivalents of bispidine to give an organolithium species that was trapped with triisopropyl borate according to Hoppe and co-workers' original procedure.[11] Transesterification with pinacol then gave boronate **14** (58% yield). Upon treatment with phenylmagnesium bromide and basic H_2O_2, boronate **14** was converted into alcohol (*R*)-**15** in 60% yield and with 87:13 e.r., which is a respectable enantioselectivity given that only 0.2 equivalents of (−)-sparteine was used.[15] This two-ligand approach to catalytic asymmetric deprotonation is necessary as (−)-sparteine is not turned over in the absence of a second diamine.



Scheme 9. Synthesis of aryl alcohol (*R*)-**15** from alkyl carbamate **13** using only 0.2 equivalents of (−)-sparteine.

In summary, two different ways of directly arylating enantioenriched carbanions generated from *N*-Boc pyrrolidine **1** and *O*-alkyl carbamates **2** have been presented. Indeed, with the recent developments in asymmetric deprotonation, either enantiomer of the products can be accessed using substoichiometric amounts of chiral diamines. Furthermore, although this Highlight has focused on the asymmetric arylation of carbanions, transformations that could not previously be achieved, there is much scope for the development of both types of methodology. For the asymmetric deprotonation–Negishi coupling, many other types of coupling partners could be envisaged. With the 1,2-metalate rearrangement method, the scope has already been expanded to include the transfer of non-aryl substituents, which is particularly useful for sterically hindered groups, such as *t*Bu, that could not be introduced by deprotonation trapping. Finally, the methodology summarized herein now appears suitable for application in total synthesis, as demonstrated by Kocienski's synthesis of (*S*)-(−)-*N*-acetylcolchinol.

Published online: March 10, 2008

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